

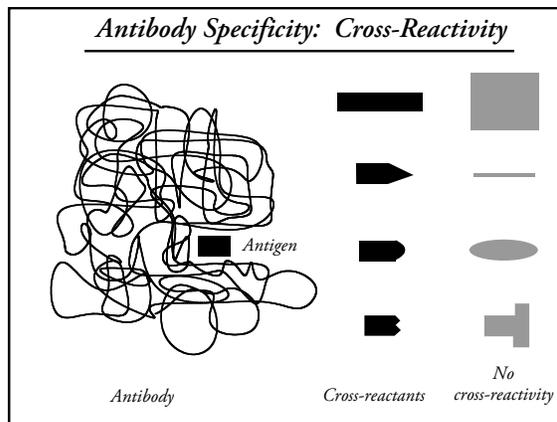
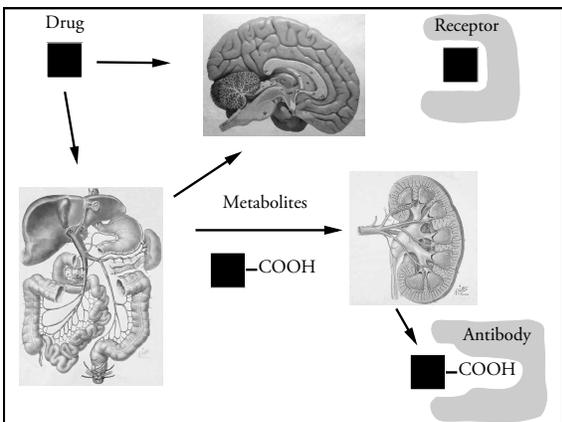
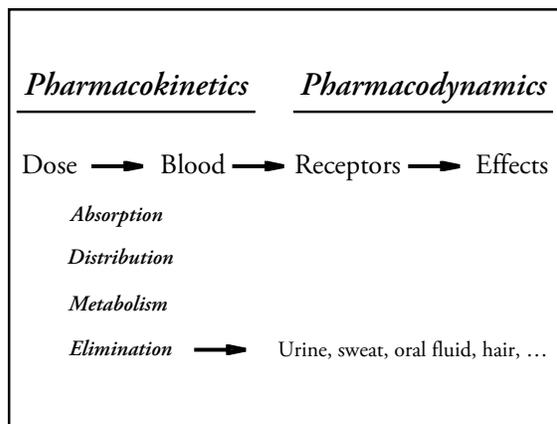
New Drugs of Abuse: Detection and Challenges

Dr. Leo Kadehjian
Palo Alto, California

Mother Nature vs. Chemists

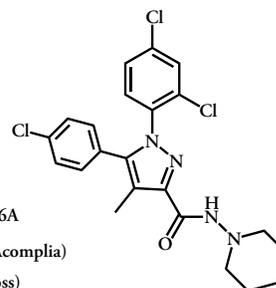
<u>Stimulants</u>		<u>Sedatives</u>	
Caffeine	Amphetamines	Ethanol	Barbiturates
Nicotine	MDMA		Benzodiazepines
Cocaine			Methaqualone
Ephedrine			
Khat			
<u>Opiates</u>		<u>Hallucinogens</u>	
Morphine	(Heroin)	Mescaline	(LSD)
Codeine	(Oxy-, Hydro-)	Psilocybin	PCP
	Methadone, LAAM	Marijuana	
	Fentanyl		
	Meperidine		

- ### New Drugs: "Designer Drugs" "Legal Highs"
- ▶ 1980s Fentanyl
 - ▶ Late 1980s Ring-substituted phenethylamines
 - ▶ 1990s Tryptamines ("Foxy")
 - ▶ 2000s
 - Salvia divinorum
 - Synthetic opioids, cocaine derivatives
 - Synthetic cathinones
 - "Spice", synthetic cannabinoids
 - Benzylpiperazines



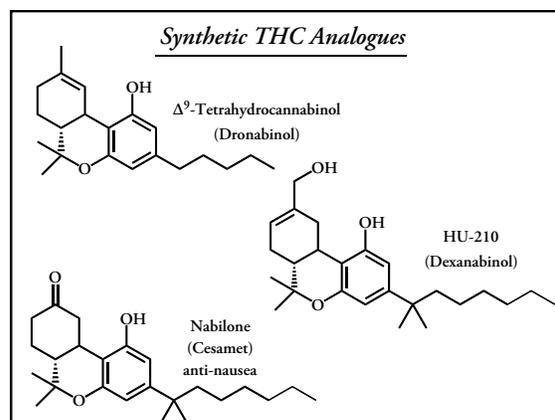
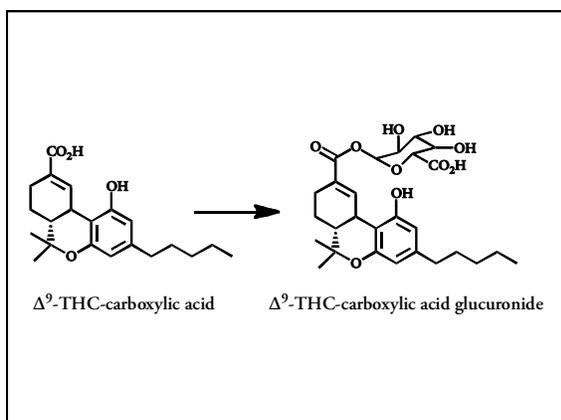
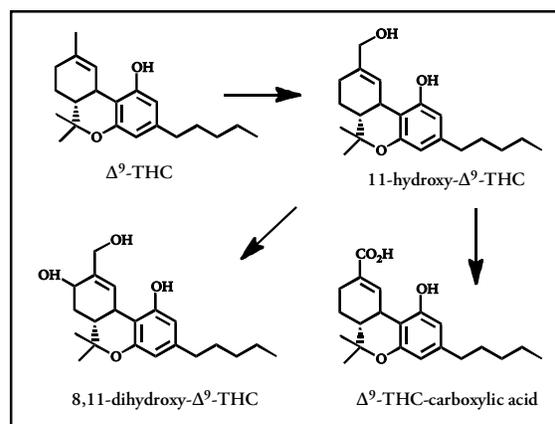
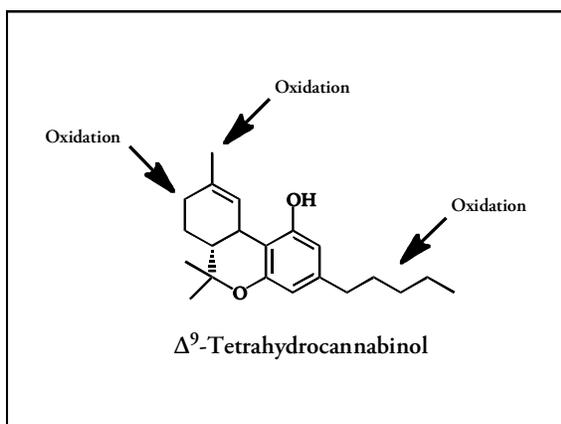
Cannabis History

- 2327 BC Documented use of cannabis, Nung dynasty
- 1937 Marijuana Tax Act
- 1964 Identification of Δ^9 -THC
- 1970 Controlled Substances Act: Marijuana Schedule I
- 1985 Marinol (dronabinol) FDA approved: nausea
- 1988 CB₁ receptor identified
- 1990 CB₁ receptor cloned
- 1992 Endogenous ligand "Anandamide" ("Internal bliss")
- 1993 CB₂ receptor cloned
- 1994 CB₁ receptor antagonist SR 141716A, Rimonabant (Acomplia)
- 1996 Medical marijuana initiatives (CA, AZ)
- 1998 CB₂ receptor antagonist SR 144528



SR 141716A
Rimonabant (Acomplia)
(Weight loss)
CB₁ antagonist

10/08 Removed from European market (psychiatric side effects)



Synthetic Cannabinomimetics Nomenclature

HU = Hebrew University

JWH = John W. Huffman, Clemson University

WIN = Sterling-Winthrop

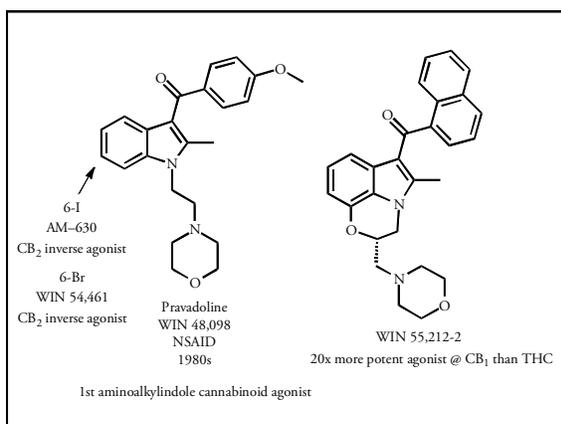
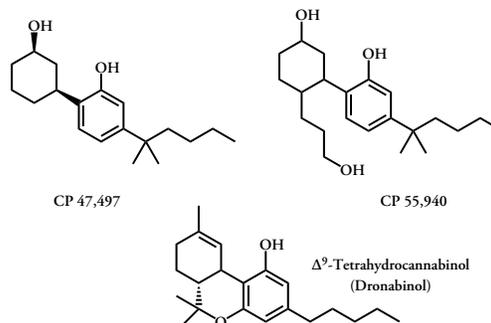
SR = Sanofi Research

AM = Alexandros Makriyannis, University of Connecticut,
Northeastern University

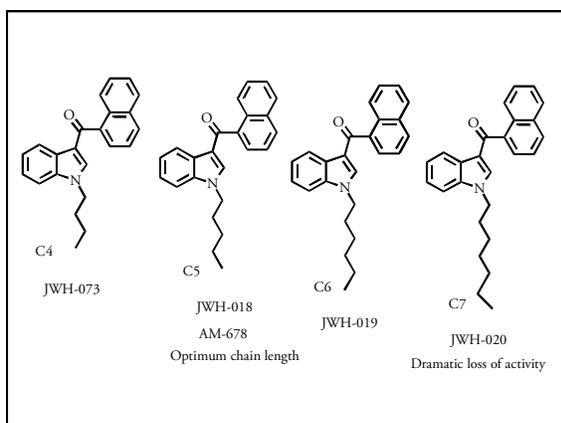
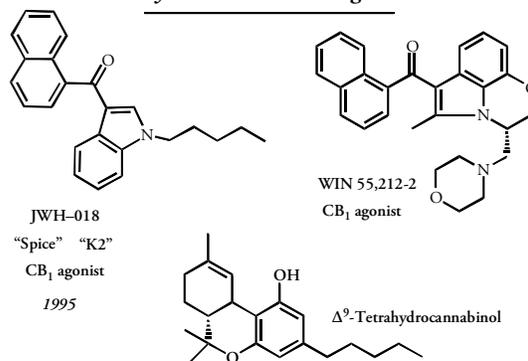
CP = Pfizer

AB = Abbott

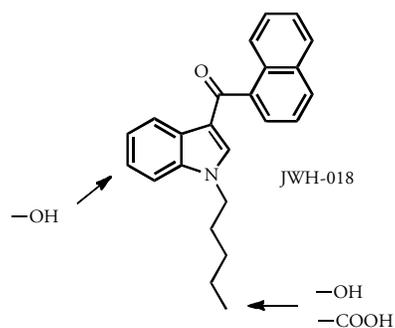
Synthetic THC Analogues



Synthetic THC Analogues



Synthetic Cannabinomimetics Metabolism



Metabolism of Synthetic Cannabinomimetics

<i>in vitro</i> , rat liver microsomes	Q. Zhang <i>et al.</i> , 2006
<i>in vivo</i> , rats, urine	T. Kraemer <i>et al.</i> , 2009
<i>in vivo</i> , human (2) dosing	V. Auwärter <i>et al.</i> , 2009
<i>in vivo</i> , human (3) users, urine	T. Sobolevsky <i>et al.</i> , 2010
<i>in vitro</i> , human liver microsomes	A. Wintermeyer <i>et al.</i> , 2010
<i>in vivo</i> , human (2) dosing, serum	J. Teske <i>et al.</i> , 2010
<i>in vivo</i> , rats, human (2) users	A. Grigoryev <i>et al.</i> , 2011
<i>in vivo</i> , human users	S. Beuck <i>et al.</i> , 2011
<i>in vivo</i> , human (1)	M. Möller <i>et al.</i> , 2011
<i>in vivo</i> , human (5) users	M. Hutter <i>et al.</i> , 2012

DEA Scheduling of Synthetic Cannabinoids

11/24/10	DOJ, DEA	75 FR 71635	Notice of Intent Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids Into Schedule I
3/1/11	DOJ, DEA	76 FR 11075	Final order Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids Into Schedule I
3/1/12	DOJ, DEA	77 FR 12508	Notice of Proposed Rulemaking Schedules of Controlled Substances: Placement of Five Synthetic Cannabinoids Into Schedule I

“Spice” Resources

- ▶ *Synthetic Cannabinoids and ‘Spice’ (2009)*
www.emcdda.europa.eu/publications/drug-profiles/synthetic-cannabinoids
- ▶ *Understanding the ‘Spice’ Phenomenon (2009)*
www.emcdda.europa.eu/publications/thematic-papers/spice
- ▶ J.W. Huffman, Clemson University, SC
45 papers on cannabinoids, synthetics

Khat (*Catha edulis* Forsk., *Celastraceae*)

- ▶ Perennial, evergreen tree, @ 1500–2500m
- ▶ Ethiopia (tschat), Yemen (qat), East Africa, Somalia, Kenya (miraa)
- ▶ Banned: Saudi Arabia, U.S., U.K., other Arab and European countries
- ▶ Yemen: 90% of males, 60% of females use regularly, students (exams)
- ▶ Yemen: \$2b/year spent on khat (50% of family income), 40% of irrigated land, 33% of GNP on cultivation, export, use
- ▶ Kenya trade w/Somalia: \$100m
- ▶ Djibouti: Import tax 10% of gov’t budget

“... in Djibouti, where khat is flown in daily, it is commonly said that the effects of the drug begin when the incoming plane is heard in the sky.”

P. Kalix and O. Braenden, 1985

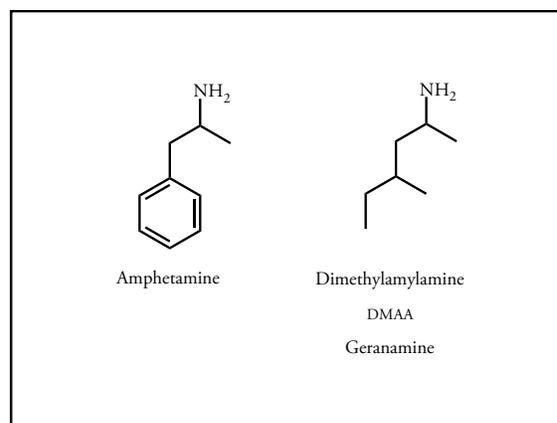
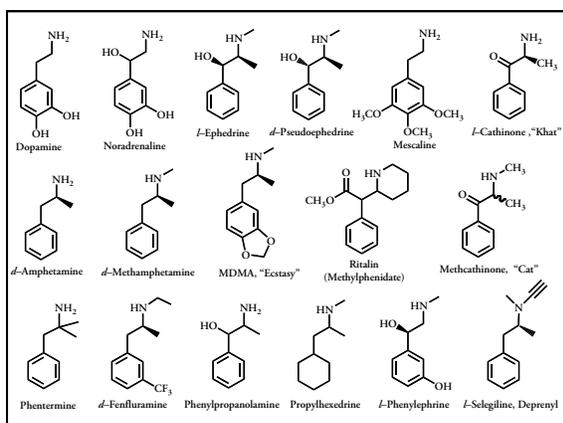
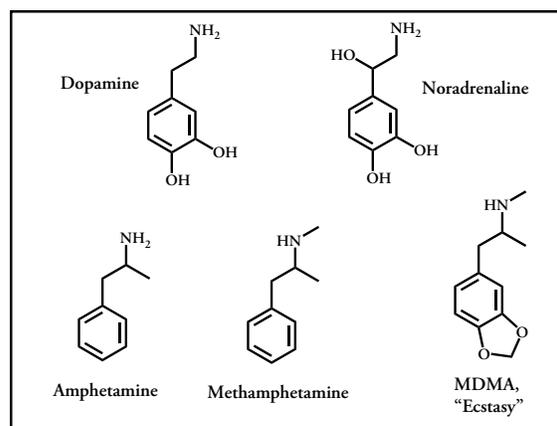
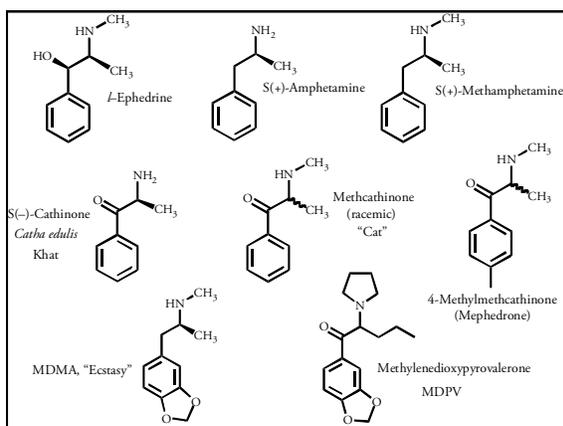
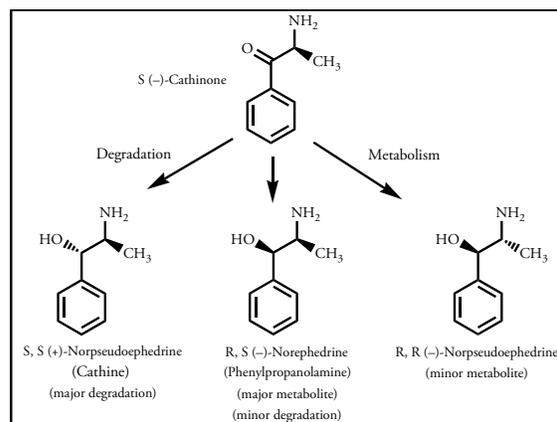
“It is what gives us our power, without khat Yemen is nothing.”

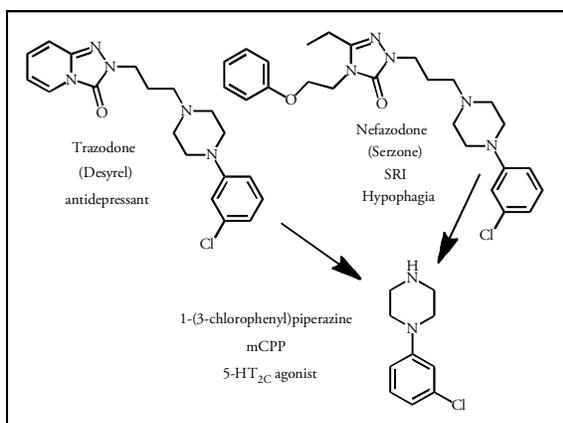
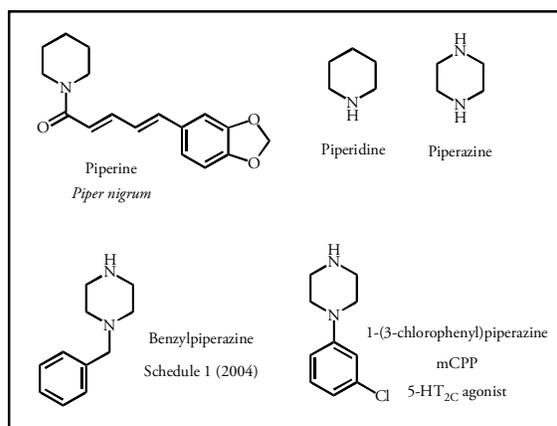
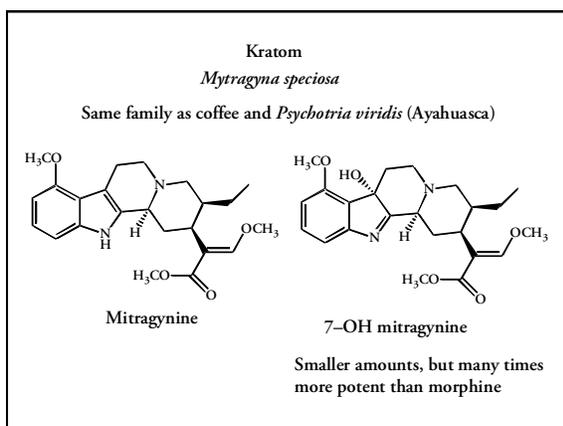
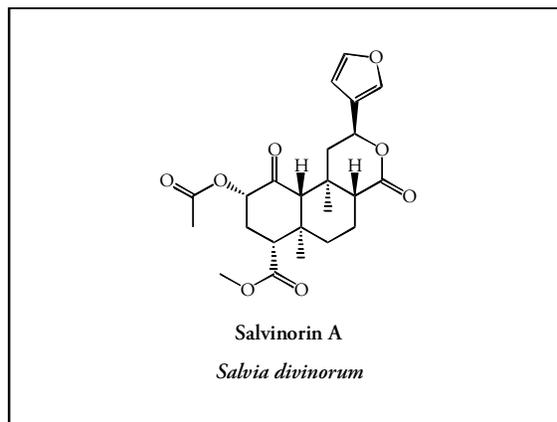
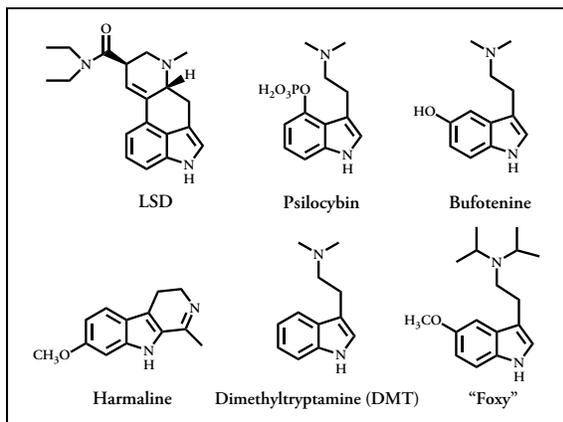
Yemeni government official
quoted in Lancet

P. Kandela, 2000

“... in terms of pharmacology, the use of the stimulant khat is tantamount to the use of amphetamine.”

P. Kalix, 1984





New Drugs Resources

- ▶ NIDA: www.drugabuse.gov
- ▶ DEA: www.justice.gov/dea/index.htm
 Microgram Journal, Bulletin, Controlled Substances
- ▶ European Monitoring Centre for Drug and Drug Addiction:
www.emcdda.europa.eu
 since 1997 Early-Warning System (110 substances identified)
 2009 24 new substances
- ▶ Erowid: erowid.org
- ▶ MAPS.org Multidisciplinary Association for Psychedelic Studies
- ▶ Lycaenum.org Entheogen database

Prescription Drug Abuse

Dr. Leo Kadehjian
Palo Alto, California

Abused Prescription Drugs

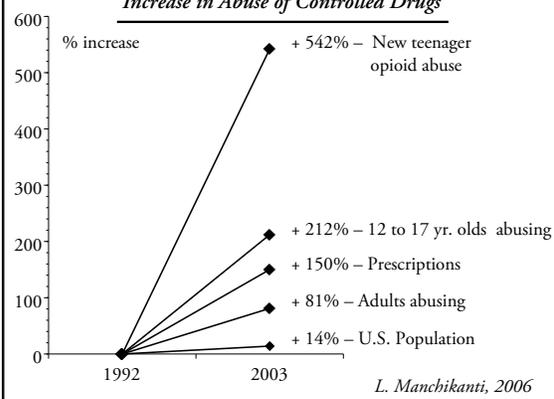
Opioids	CNS Depressants	Stimulants
Morphine, codeine, etc.	Benzodiazepines	Cocaine
Oxycodone (OxyContin)	Non-benzos	Amphetamine
Buprenorphine	Barbiturates	Methamphetamine
Methadone		Methylphenidate
Fentanyl		
Meperidine	<u>OTC</u>	<u>Other</u>
Propoxyphene	Ephedrine, etc.	Carisoprodol
	Dextromethorphan	Ketamine
	Antihistamines	Steroids

United States' Drug Consumption

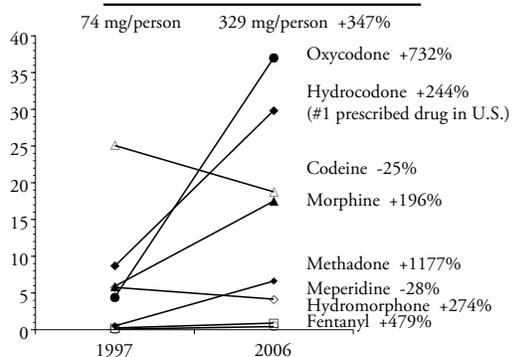
- ▶ 4.6% of world population
- ▶ Consumes 2/3 of illicit drug supply
- ▶ Consumes 80% of global opioid supply
- ▶ Consumes 99% of global hydrocodone supply

L. Manchikanti and A. Singh, 2008

Increase in Abuse of Controlled Drugs



Retail Sales of Opioids (millions of grams)

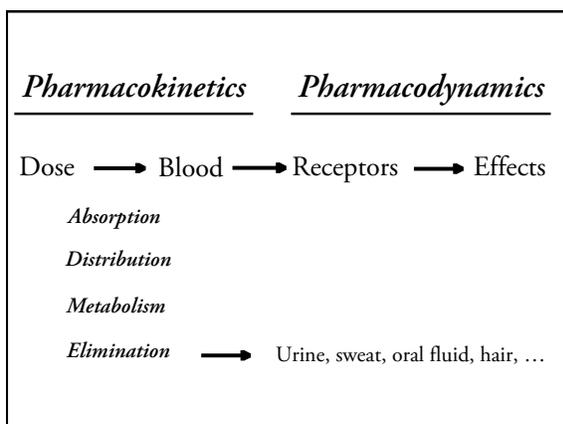
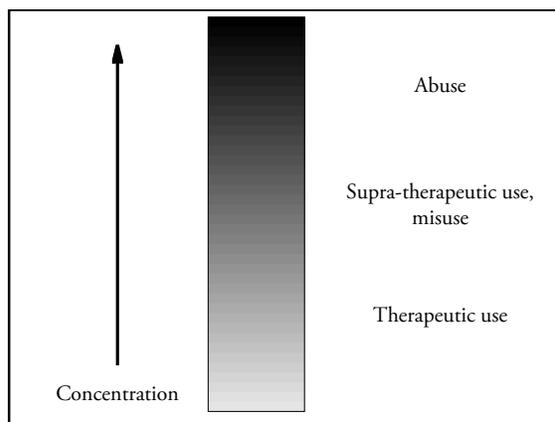
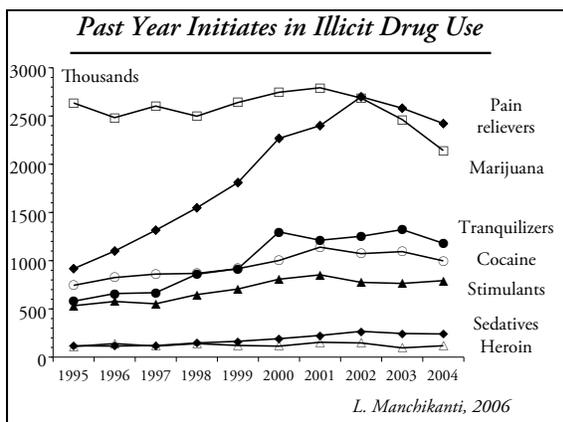


Oxycodone per Capita

DEA 2013 Oxycodone Production Quota: 135,000 kg

2011 U.S. Population: 311,591,917

$$\frac{135,000 \text{ kg}}{311,591,917 \text{ persons}} = 422 \text{ mg/person!}$$



Urine Drug Concentrations (ng/mL): 10,922 Chronic Pain Patients

	Mean	Median	Range
Amphetamine	10,163	3,910	196-93,372
Methamphetamine	15,674	1,854	108-329,591
Oxycodone	7,599	2,690	100-341,009
Oxymorphone	4,930	1,637	100-188,306
Hydrocodone	2,953	1,380	100-405,020
Hydromorphone	1,062	476	100-64,526
Methadone	4,167	2,179	104-93,322
Meperidine	3,086	1,138	195-52,216
Normeperidine	3,490	1,375	124-19,908

E. Cone et al., 2008

- Resources on Prescription Drug Abuse**
- ▶ National Institute on Drug Abuse (NIDA), www.drugabuse.gov/drugpages/prescription.html
 - ▶ National Survey on Drug Use and Health (NSDUH), www.oas.samhsa.gov/nsduh.htm
 - ▶ Monitoring the Future, www.monitorthefuture.org
 - ▶ Drug Abuse Warning Network (DAWN) www.dawninfo.samhsa.gov/default.asp
 - ▶ Treatment Episode Data Set (TEDS) www.oas.samhsa.gov/dasis.htm#teds2
 - ▶ Community Epidemiology Working Group (CEWG), www.drugabuse.gov/about/organization/CEWG/CEWGHome.html
 - ▶ Medline (PubMed), www.pubmed.gov